

Absolute and Relative Risk of Aggressive Prostate Cancer in Men with a Positive Family History; A systematic-review

By

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Abstract

Background: In May 2012, the United States Preventive Services Task Force recommended against PSA-based screening in men of all ages, regardless of race or family history. However, though risk of harms outweighs potential benefits in men in the general population, men at higher risk of dying from prostate cancer may have a larger mortality benefit. Although previous reviews have demonstrated that family history of prostate cancer in a first-degree relative is a risk factor for *overall* prostate cancer, this may not correspond to a higher risk of death. In this review we assess family history as a risk factor for *aggressive* prostate cancer to determine if men with family history have a potentially larger mortality benefit than average risk men.

Purpose: To determine the relative and absolute risk of aggressive prostate cancer in men with at least one affected first-degree relative

Data Sources: MEDLINE and Embase (search dates 1992 to June 2012), recent systematic reviews, reference lists of retrieved articles and suggestions from experts.

Study Selection: English-language, randomized, controlled trials, cohort studies, case-control studies and cross-sectional studies meeting eligibility criteria

Data Extraction: All studies were reviewed, abstracted and rated for quality using the STROBE criteria and supplemented with guidelines provided by Deets et al.

Data Synthesis: Three fair quality cohort studies, one fair quality and six poor quality case-control studies and one fair quality cross-sectional study demonstrated mixed results of difference of risk magnitude for aggressive prostate cancer in men with family history of prostate cancer in a first-degree relative compared to men without family history. In cohort studies reporting increased relative risk, we calculated absolute risk and attributable risk to be small.

Limitations: There is limited evidence from good quality studies addressing aggressive prostate cancer risk in men with family history. Use of surrogates, inability to assess harms and variations among study populations by region, age, co-variates and prior screening rates limits generalizability.

Conclusion: Evidence is insufficient to suggest an increase in relative or absolute risk of aggressive prostate cancer in men with an affected relative compared to men in the general population without determining family history in greater detail (age of diagnosis, cause of death, intent of treatment, etc.).

“Now, I probably won't be entering a discussion about prostate cancer screening unless my patient has a family history of prostate cancer or he expresses concern,” said general internist Christine Laine, MD, MPH, editor in chief of *Annals of Internal Medicine*.¹

Focused question

What is the relative and absolute risk of *aggressive* prostate cancer in men aged 40-70 years who have a family history of prostate cancer in at least one first-degree relative compared to men without such family history?

Introduction

Statement of Purpose

On March 22, 2012, the United States Preventive Services Task Force (USPSTF) recommended against prostate specific antigen (PSA)-based screening for prostate cancer in all men, regardless of age, race or family history.² These recommendations were, in a large part, based on results from two large randomized trials which showed only a small^{3, 4} or no mortality benefit^{5, 6} from PSA-based screening. Risk of harms outweighs potential benefit in average risk men, “high-risk” men (men with a family history and African American men), may have larger mortality benefit. Although randomized trials are needed to evaluate PSA-based screening in “high-risk” groups, determining the magnitude of risk for men with family history compared to men in the general population is a prerequisite. Previous reviews have documented family history as a risk factor for *overall* prostate cancer;⁷⁻⁹ however, it is important to distinguish *aggressive* – clinically significant – from *indolent* – clinically insignificant – prostate cancer. We will use the term *overall* prostate cancer to refer to the sum of indolent and aggressive prostate cancer. We will define aggressive prostate cancer below (see Defining Aggressive Disease). The

purpose of this review is to examine and accurately report¹⁰ the level of evidence on risk of *aggressive* prostate cancer in men with a family history compared to those without.

Background

Prostate Cancer in the “PSA-era”

The incidence rates of prostate cancer in the United States increased dramatically as PSA-based screening became clinically accepted, peaking at nearly 250 cases per 100,000 in the early 1990’s.¹¹ However, despite its widespread use, the role of the PSA in screening for prostate cancer has become and will likely continue to be controversial. In 2009, the publication of two large, randomized controlled trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the United States Prostate, Lung, Colorectal and Ovarian (US PLCO) studies showed small³ and no⁵ survival benefit, respectively. These trials continued to yield conflicting results with continued patient follow-up.^{4, 6} In May 2012, the United States Preventive Services Task Force recommended against PSA-based screening with the finding that the risk of harms outweighed the benefits.^{2, 12} Based on data from the ERSPC, an estimated 1055 men need to be screened to prevent 1 death from prostate cancer.³ However, the number needed to screen may be smaller for “high-risk” men, such as those with a positive family history.

Scope of Review

In this review, we examined the evidence on risk of *aggressive* – clinically significant – prostate cancer in men with a family history. This review is meant to inform practitioners and allow for better more complete discussion with their patients with affected relatives. It is also intended assist in assisting the need for randomized trials evaluating screening in this group of men. Given the current uncertainty of screening in

these men, a review of the evidence specifically regarding *aggressive* disease is imperative for health care providers in promoting informed discussions with patients regarding derivation of benefit or avoidance of harm of screening and treatment. Furthermore, we also hope that by characterizing the risk magnitude in these men, we may gain insight into the potential benefit of screening in this group and determine if it is greater than for men in the general population.

Recommendations of Other Associations

The American Urological Association (AUA), American Association of Clinical Urology and other individual experts in the field have been critical of the new guidelines, citing concerns about study quality and emphasizing the need for more complete understanding of the clinical contexts and consequences.¹³⁻¹⁷ With regards to men with positive family history, both the AUA and American Cancer Society (ACS) recommend offering screening to men at age 40 and prior to age 50, respectively.^{18, 19} The American Academy of Family Physicians (AAFP) and the United States Preventive Services Task Force recommend against screening for men of all ages, regardless of race or family history.^{2, 20} The disagreement among medical professional societies will contribute to the challenge patients and their providers face in the context of a shifting preventive care paradigm.

Epidemiology

Prostate cancer remains the most commonly diagnosed solid tumor and the second leading cause of cancer-related death in American men.²¹ In the “PSA-era” the risk of being diagnosed with prostate cancer has increased, however the risk of dying from prostate cancer has remained relatively constant.²² A man born today has a 16% chance of

being diagnosed with prostate cancer and a 3% chance of dying from the disease.²³ In 2011, an estimated 240,890 men were diagnosed with prostate cancer and 33,720 men died from the disease.²³ Although these estimates do not distinguish *aggressive* from *overall* disease, both prostate cancer diagnosis and mortality clearly represent a considerable burden for the United States population. The epidemiology of *aggressive* prostate cancer is unclear. The prevalence of overall prostate cancer in men with an affected relative is estimated at 2- to 4- fold greater than the general population.²⁴ The prevalence of aggressive prostate cancer in men with a family history is the subject of our review.

Prostate Cancer Risk Factors

There are several risk factors for overall prostate cancer that are supported by a strong body of evidence, while for others the evidence is less robust. We discuss all known risk factors for prostate cancer below as the implications of cumulative risk may be important clinically. Note that we will discuss risk of *aggressive* disease when known, however for many factors the association is unclear.

Age

Age has a stronger relationship with prostate cancer than perhaps any other malignancy. Prostate cancer is exceedingly rare prior to age 40 and occurs most frequently in individuals over 60 years of age.²⁵ Estimated incidence rates of prostate cancer in men 40-49 is 50-100 per 100,000 compared to 600-800 per 100,000 in men aged 60-69.²² While these incidence rates apply to those prostate cancers diagnosed clinically (by PSA-based screening and or with symptoms), the prevalence of *occult* prostate cancer is much greater. Autopsy studies are highly variable but have shown that that up to 43% of men

aged 41-50, 46% aged 51-60, 70% aged 61-70, and 83% aged 71-80 have histological evidence of malignancy with no clinical evidence of disease.²⁶

Ethnicity

Ethnicity is also considered to increase risk of prostate cancer. African American men are 1.6 times as likely to develop the disease than Caucasian, Hispanic and Asian men (incidence rates of approximately 226 and 145 cases per 100,000 person-years for African American men and Caucasian men, respectively) and are 2.3 times more likely to die from prostate cancer.²² Additionally, African Americans are more likely to be diagnosed with more aggressive disease at an earlier age compared to Caucasian men.^{27, 28} However, the role of disparity in healthcare access and trust of healthcare professionals may confound the differences in incidence and mortality.²⁹ African American men may also be more likely to be diagnosed due to –on average – higher measured PSA levels compared to Caucasian men and when stratified by age, access, stage at diagnosis, some studies show ethnicity may not independently have implications for outcomes.³⁰

Family History

Family history of prostate cancer in a first or second degree relative is considered to increase risk of *overall* prostate cancer. The association with *aggressive* prostate cancer is unclear and thus the reason for this review. With regard to risk of *overall* prostate cancer, estimates of relative risk compared to men without family history vary as widely as 1.4 to 17.8 in first-degree relatives.⁹ We will address family history as a risk factor for *overall* prostate cancer below in our discussion of previous systematic reviews and meta-analyses. Specific genotypes (BRCA 1 and 2 mutations, HOXB13) are discussed in the Genetics of Prostate Cancer section.

Other Factors

Androgens have also been shown to increase risk for overall prostate cancer. Use of 5-alpha-reductase inhibitor, finasteride, was shown to decrease risk of cancer in the Prostate Cancer Prevention Trial (PCPT).³¹ Many other factors have been reported in the literature to increase prostate cancer risk. These risk factors include animal fat, vegetable matter, soy, alcohol, coffee, obesity, insulin and insulin-like growth factor, physical activity, vasectomy, ejaculatory frequency, ultraviolet light exposure, diagnostic radiologic procedure, external beam radiotherapy, prostatitis with *Trichomonas*, XMRV virus, exposures such as Agent Orange, Chlordecone, medications such as NSAIDs and statins, and vitamins and minerals including vitamin E, folic acid, selenium, zinc, calcium and vitamin D.³² The quality and clinical contribution of these studies investigating these associations is beyond the scope of this review.

Genetics of Prostate Cancer

Numerous studies report risk of prostate cancer is strongly affected by family history, particularly early onset disease. Several studies, including family studies and genome-wide association studies have suggested that prostate cancer has a strong genetic component, an estimated 5-10% of prostate cancer cases are believed to be due to “high-risk” genetic factors and/or susceptibility genes.³³ Generally, it is believed that there are three forms of prostate cancer. *Sporadic* prostate cancer occurs randomly in the general population, *familial* cancer occurs in unpredictable clusters of disease within multiple families and *hereditary* prostate cancer occurs in predictable clusters within individual families; among hereditary cancer, some have been shown to occur prior to age 50 and are associated with rapidly aggressive disease.³⁴ Classically, hereditary prostate cancer is

considered to be passed on by autosomal dominance transmission and represents as many as 43% of prostate cancers diagnosed before age 55, but only 9% of prostate cancers in men overall.³⁵

In a recent review of 8 prostate cancer large linkage studies that evaluated 4,600 cases of prostate cancer from 1,293 kindreds, a lack of consistency was found among genetic models; Easton et al. concluded that prostate cancer is genetically complex and would require large family sets to draw reliable linkages.³⁶ Another review found that several genomic regions are linked to high-grade tumors, but the prevalence and interaction with diet and environment are unknown.³⁷ However, certain predispositions for overall prostate cancer have recently been evaluated with consistent findings. Cohort studies show HOXB13, BRCA1 and BRCA2 mutations place individuals at higher risk.³⁸
³⁹ A population-based study of prostate cancer cohort in Seattle reported 22 single nucleotide polymorphisms (SNPs) found to be significantly associated with prostate cancer-specific mortality, but these results await validation and replication.⁴⁰

In summary, although the genetics of prostate cancer is a rapidly developing field, much remains unknown. While BRCA mutations may have implications for overall prostate cancer, few studies consistently show specific genotypic predispositions for aggressive disease. Furthermore, if genetic contexts that predispose to aggressive prostate cancers can be validated, the prevalence in the general population is unclear. Finally, the benefit of PSA-based screening in these populations, if they exist and are reliably detectable, is unclear.

Detection to Diagnosis

Since the PSA-based screening became widespread, many prostate cancers are detected asymptotically. Other modes of detection include digital rectal examination(DRE) or with symptoms. On DRE, prostate cancers are asymmetric areas of induration or nodules detected by manual examination. Symptoms suggestive of prostate cancer include new onset urinary urgency, nocturia, frequency, hesitancy, or new onset erectile dysfunction. Bone pain may be a presenting symptom in a small percentage of men with metastatic disease. Any of the above presentations warrants a prostate biopsy. Prostatic biopsy varies with regard to procedure; anatomic approaches include transrectal, transperineal and transurethral resection. Though it has many risks, prostate biopsy is considered to be a minimally invasive procedure performed in the office setting. Prophylactic antibiotics are recommended prior to biopsy to lower incidence of post-biopsy bacteriuria.⁴¹ Local anesthesia can be given to reduce patient discomfort. Most often in current practice, an extended core (5-7 specimens from each side of the gland or occasionally up to 18 cores) or saturation biopsy (up to 24 core samples) are performed to observe neoplastic cells within the gland.

PSA Test Characteristics

As a screening test for early detection of prostate cancer, the PSA has many limitations. The sensitivity of the PSA test for high-grade disease is estimated at 51% using a cut-off of 4.0 ng/mL; the test also has poor positive predictive value as less than one in three men with an elevated PSA will have any grade of prostate cancer on biopsy.⁴² Although the test has a specificity of 90% at 4.0 ng/mL,¹⁸ the PSA has a false-positive rate of approximately 80% at cut-offs between 2.5 to 4.0 ng/mL.⁴ In the PLCO trial, men in the screening group had a 12.9% chance of receiving at least 1 false-positive test after

undergoing 4 PSA tests and a 5.5% risk of having at least 1 biopsy due to a false-positive.^{2,6} Although increasing and decreasing PSA cut-offs would improve specificity and sensitivity, respectively, there is no PSA level at which a man can know for certain he is without a life-threatening prostate cancer.⁴³

Efforts to improve the ability of the test to detect early disease have included use of PSA velocity, density and free-to-total PSA ratios.⁴⁴⁻⁴⁶ Use of PSA velocity, while predictive of prostate cancer, does not appear to improve detection of high-grade disease and tends to increase biopsy rates.⁴⁷ PSA density may improve sensitivity and decrease unnecessary biopsies, but is limited in clinical applicability as it requires prostatic volume measurement with ultrasound or MRI.⁴⁵ Similarly, free PSA is only considered clinically useful at extreme values and is not standard practice.⁴⁶ Recently, urinary biomarkers including PCA3, alpha-methylacyl-CoA racemase, the TMPRSS2-ERG fusion gene and microseminoprotein-beta have been proposed for early detection of prostate cancer,⁴⁸ however to our knowledge these tools await validation and have not yet been evaluated in randomized trials.

Outcomes of Screen-detected and Overall Prostate Cancer

The USPSTF recommendation statement described three categories of men with screen-detected prostate cancers: those who will die despite early detection and intervention, those who would not have died regardless of screening, and those in whom early detection and intervention may have a mortality benefit.² In average risk men, an estimated 5 in 1000 die of prostate cancer without screening compared to 4-5 in 1000 with screening.^{2,4} The fact that screening has been shown to have only a small potential benefit is likely attributable to several factors, including limited utility of PSA-based screening

and advances in treatment. Additionally, it may be that particularly aggressive tumors are largely undifferentiated and therefore do not produce PSA. An estimated 25% of men with PSA below 4 have Gleason scores of 7 or more, 12.5% of men have high-grade disease with PSA of 0.5 ng/mL or less.⁴⁹ However, these estimates may not be applicable for men at higher risk for overall or aggressive prostate cancer.

TNM Stage and Gleason Score

Prostate cancer is staged with the TNM system. Of some importance to our review, the TNM system underwent changes in 2002 and 2010. The most recent change incorporated Gleason score as the standardized histopathology grading system (previous systems did not specify the system to be used for grading histopathology). The Gleason score has also experienced an “upward migration” over the study period, as the percentage of higher grade Gleason has increased over time which is known as the Will Rogers phenomenon.⁵⁰

Defining Aggressive Disease

In men with localized disease, the TNM Stage, Gleason score and PSA level prior to treatment are the most important prognosticators, predicting both probability of distant disease and survival. Additionally, these measures also guide therapeutic approach and treatment modality. For local disease, radical prostatectomy and external beam radiation therapy are both employed in combination or as single modalities, with or without hormonal therapy. Advanced (nodal positive) disease requires more intensive regimens and metastatic disease is treated with palliative hormonal and radiotherapy. A more detailed description of treatment options for local and advanced prostate cancer is beyond the scope of this review but can be found in the NCCN guidelines.⁵¹

The TNM Stage refers to tumor size, nodal status and presence of distant metastases. While a T1b tumor has a 5-year survival of 85%, tumors greater than T2 have 5-year survivals of less than 66%.⁵² The Gleason score reflects the degree of histopathology and predicts the likelihood of organ confined disease with implications for survival. A tumor's overall Gleason score is a composite of the two most predominant growth and differentiation grades – where grade 1 is the most and grade 5 is the least differentiated – present within a tissue sample.⁵³ While a Gleason score of less than 7 correlates with a 10-year survival rate of 98.4%, a Gleason score of 8 or greater corresponds to a 10-year survival rate of less than seventy-percent.^{51, 54} Similarly, PSA levels at the time of diagnosis correlate with the aggressiveness of disease and mortality. For a PSA of 10 or less, the 5-year survival is approximately 81% compared to 51 and 31% at PSA values 20-30 and greater than 30 ng/mL, respectfully.⁵²

The 2010 TNM Anatomic Stage/Prognostic Groups are provided in Table 1. As shown in the table, TNM Stage and Gleason score both have “thresholds” at which Anatomic Stage and thus prognosis, change significantly. For the purposes of our review, we required an aggressive cancer to have at least 1 of these “advanced” characteristics. Based on TNM 2010 Anatomic Stage, aggressive disease had *at least* one of the following tumor characteristics: TNM Stage T3a or greater, Gleason Score of 7 or greater, or pretreatment PSA of 20 ng/mL or more.⁵⁵⁻⁵⁷

Table 1. RTOG prognostic model for disease-specific survival in early stage prostate cancer⁵⁸

	5 year (%)	10 year (%)	15 year (%)
Group 1	96	86	73
Group 2	94	75	61
Group 3	83	62	39
Group 4	64	34	27
Group 1 – Gleason score 2-6, T1-2, Nx			
Group 2 – Gleason score 206, T3, Nx, or Gleason score 206, N+, or Gleason score 7, T1-2, Nx			

Burden of Suffering

Population-based studies estimate the prevalence of family history of prostate cancer to be approximately 5-7%.^{59, 60} Men with a positive family history have increased risk perception compared to men without a family history which can lead to depression and worry that affects daily life.⁶¹ Population-based studies show that while 60% of men with first-degree relatives worry little or not at all about prostate cancer, the remaining 40% worry to an extreme degree.⁶² A review on PSA-based screening “uptake” in men with family history of prostate cancer reported 50-95% of men received PSA-based screening with variations by socioeconomic status and race.⁶³

Harms of PSA-based Screening in Average Risk Men

Prostate biopsy is usually uncomplicated and well-tolerated, but harms must be considered. Harms of prostatic biopsy include anxiety, infection, pain, bleeding, urinary obstruction and tumor seeding, although this is unusual. Risk of infection is lowered with single dose of prophylactic antibiotic therapy, but has contributed to overuse of fluoroquinolone antibiotics.⁴¹ Men on anticoagulant therapy are recommended to temporarily stop the medication prior to biopsy. Most bleeding is self-limited and requires no intervention. Hematuria and/or hematospermia occur in as many as 50% of men and in 23%, it lasts more than 3 days.⁶⁴ Retrospective studies show up to 3.5% of men develop post-biopsy fever, but less than 1% required hospitalization.⁶⁴ Most men with screen-detected cancers will elect to have treatment.⁶⁵ Harms associated with treatment depend on the modalities employed. Up to 0.5% of men will die within 30 days of radical prostatectomy (similar to rates of any major operation), 3-7% will have serious

complications and 20-30% of men will experience erectile dysfunction, urinary incontinence or both after 10 years; radiation therapy can also increase risk of erectile, bowel and bladder dysfunction.⁶⁶

Potential Harms in Men with Family History

If family history is associated with aggressive disease, it could be the harms of screening become outweighed by the benefits of early detection and intervention. However, if a review of the literature reveals no or little increase in risk of aggressive prostate cancer, men with a family history could represent a subgroup at high risk for harms of screening, diagnosis and treatment.

Previous Systematic Reviews and Meta-Analyses

As mentioned above previous reviews have identified risk of *overall* prostate cancer in men with a family history. In 2003, Johns and Houlston identified 13 case-control and cohort studies assessing risk for categories of family history (father, son); meta-analysis showed pooled relative risk of 2.5 (confidence interval 2.2 to 2.8) of overall prostate cancer in first-degree relatives.⁶⁷ Also in 2003, Zeegers et al. published a meta-analysis on 33 studies and found a “recurrence risk ratio” of 2.53 (2.24-2.85) of *overall* prostate cancer for first-degree family members, more pronounced in men with an affected brother than father. Bruner et al. also published a meta-analysis of 24 studies in 2003, reporting a relative risk 2.22 (2.06-2.40) for first-degree relatives for *overall* prostate cancer.⁹ In 2010, Madersbacher et al.⁶⁸ and Robool et al.⁶⁹ both conducted informal systematic reviews reporting strong evidence of an association between family history of prostate cancer and increased risk of developing the disease.

One concern with previous reviews is the risk of selection bias. Logically, men with a positive family history are more likely to be aware of the disease and therefore more likely to be screened. Because indolent prostate cancer is present in such a large percentage of the population and PSA is an inaccurate test, this group of men may, therefore, be more likely to be *overdiagnosed* with a prostate cancer that may have never caused symptoms during their lifetime. In this review we limit our report to risk of *aggressive*, clinically *significant* disease in men with a family history of prostate cancer in at least one first-degree relative.

Summary

Age, race and family history are considered to be the three most valuable risk factors for prostate cancer. PSA-based screening is the central modality for early detection and intervention of prostate cancer. In May 2012, the USPSTF found that the risk of harms outweighed potential benefits of PSA-based screening for average risk men, however this may not be true for “high-risk” groups. The potential for a mortality benefit in high risk groups depends in part on family history as a risk factor for *aggressive* disease. The purpose of this report is to review the literature and examine risk of *aggressive* disease in men with a family history of prostate cancer in a first-degree relative compared to men in general population.

Key Question:

This review aims to address the following questions:

1. What is the relative risk of aggressive prostate cancer in men with a positive family history?

2. If there is an increased relative risk, what is the absolute risk of aggressive prostate cancer in men with a positive family history?

Methods:

Literature Search

We developed a search strategy to address our question with the assistance of a research librarian. We conducted a systematic search of MEDLINE and Embase. Both MEDLINE and Embase were accessible through the University of North Carolina at Chapel Hill's Health Science Library. See Appendix for detailed description of search strategy.

Study Eligibility:

To be included in the review, studies must have identified the study population, intervention, comparator group, outcomes, time allotted for outcome development and be within the time range specified for published literature and have described the study design. Figure 1 presents the eligibility criteria with the PECOTTS framework.

Figure 1: Focused Question in PECOTTS framework

Population:	Men aged 40-70 who have had at least one first-degree relative diagnosed with prostate cancer
Exposure	Reliable establishment of family history
Comparator	US men aged 40-70 without family history of prostate cancer in a first-degree relative
Outcome	Diagnosis of aggressive prostate cancer as defined by one of the following: <ol style="list-style-type: none">1. Gleason score ≥ 72. TNM stage T3 or greater3. Pretreatment PSA ≥ 204. Prostate Cancer Death

Time allotted for outcome	40 years
Time period for literature search	1992 - 2012
Study Designs Reviewed	Randomized, cohort, case-control studies, cross-sectional

Inclusion and Exclusion Criteria

Studies were assessed with inclusion and exclusion criteria described in the PECOTTS framework, described briefly in Figure 1. The following is a detailed description of the inclusion and exclusion criteria using the PECOTTS framework.

Population

We defined for population *a priori* as all men aged 40 to 70 living in the United States. These ages were chosen because guidelines and best practice policies from nationally recognized organizations including the AUA, ACS and USPSTF have recommended or currently support screening for average and or high-risk men in this 30 year period. The magnitude of risk in this population has clinical implications. Although the benefit of screening average risk men is outweighed by risk of harms, men with a family history of prostate cancer have a *potentially different* ratio of benefits and harms. A finding of large magnitude would underscore the importance for randomized trials evaluating PSA-based screening in men with affected relatives. Conversely, if the magnitude of risk was found to be equivalent or only marginally larger in this population compared to the average population, it may be reasonable to apply the results of the ERSPC and PLCO trials to men with positive family history as well. Furthermore, if men in this population an *increased perception* of risk despite having no clinically meaningful increase in risk, men with affected relatives may be at high-risk for screening-based harms.

Disclosure of Changes – Population

As we conducted our search, two minor changes were discussed and agreed upon for the population criteria. Although we had hoped to include only men aged 40-70 years, we observed several studies which would have been included if not for the age distribution of the study population. We felt that it would be unreasonable to exclude a study if the age range did not align itself exactly with our predetermined criteria. Furthermore, many clinicians would argue that life expectancy should play a role in determining the benefits and harms of an intervention, thus in some men over 70 it could be reasonable to employ a particular intervention after considering context. The second alteration to our population criteria was nationality of study participants. We determined that it was not reasonable to exclude a study solely because the population of participants did not consist of United States men. In fact, when reviewing benefits and harms of PSA-based screening in men, the USPSTF made no such exclusion, including both randomized trials from both Europe³,⁴ and the United States.^{5,6} However, we did consider nationality of study population in assessment of external validity which was determined in part by degree to which the study findings were applicable to men with affected relatives in the US population.

Exposure and Comparator

The exposure required for inclusion was documentation of a family history of prostate cancer in at least one first-degree relative by medical records, registry, self-administered or interview-administered questionnaire. Included studies were also required to demonstrate an adequate comparator group that closely resembled cases or those exposed but had no documented first-degree relatives previously diagnosed with prostate cancer. We included studies that stratified estimations of risk by the number of first-

degree relatives, although we list these findings only in the appendix as this is beyond the scope of this current review.

Outcome

Included studies were required document aggressive prostate cancer. As determined by an abbreviated panel and discussed in the Introduction, determination of *aggressive* prostate cancer required the study to report any of the following characteristics: pathologic or clinical TNM Stage, Gleason pathologic grade, pre-diagnosis PSA or prostate cancer death. Aggressive disease was defined as Gleason score greater than or equal to 7, clinical or pathologic TNM Stage of T3a or greater, pretreatment PSA of 20 ng/mL or more or death attributed to prostate cancer. The definition of aggressive disease is modified from the 2010 TNM Staging System and corresponds to higher mortality than non-aggressive disease.⁷⁰⁻⁷²

Absolute and Relative Risk

Though clearly valuable in determining relative risk, cross-sectional and case-control designs do have limitations, one of which being the inability to provide an *absolute* risk. Relative risks, also known as risk ratios, indicate the change in risk – or probability of observing an event or outcome – associated with an intervention or patient “risk factor,” compared to a control. Relative risks provide a measure of overall probability of an outcome or event occurring, but do not provide insight into the significance of an intervention or patient factor in absolute terms. For example, though a relative risk for a particular patient characteristic could be very large, if the absolute risk associated with that characteristic is small, the *magnitude* of the change in risk, at least clinically, may be insignificant. For this reason, the magnitude of the increase in absolute

risk provides a more complete understanding of family history as a *clinically meaningful* risk factor.

Without an understanding of the absolute risk of positive family history, it could be harmful to weight this risk factor heavily when defining groups of men most likely to benefit and least likely to be harmed by screening with the PSA. Therefore, we will report or calculate absolute risk and attributable risk from all cohort studies that find a significant increase in risk of aggressive cancer in men with compared to those without affected relatives. If a study does not report a significant difference between men with and without a family history, there will be no difference in absolute risk.

Time Period in Literature

The time period over which the literature was included was between the year 1992 to the present time. This range was chosen because of the considerable prevalence in clinical practice of using PSA as a screening tool for prostate cancer. As referenced above, the introduction of the PSA as a screening tool has had a large effect on the frequency and stage at which prostate cancer is diagnosed.

Time Period Allotted for Outcome

The time allotted for the outcome to become detectable was forty years of age as the disease –regardless of any combination of risk factors – is considered to be very infrequent in men younger than 40.²² As described above, we had initially set a limit of 70 years for the outcome to occur, however we determined that setting such a limit was not clinically justifiable and additionally would have limited our search yield without sufficient reason.

Study Design

We limited the review to randomized-controlled trials, cohort studies, case-control and cross-sectional studies. Only randomized studies and cohort studies would allow for evaluation of absolute risk. Absolute risk was only calculated if a difference in relative risk was found. Case-control studies reporting odds for aggressive disease (or providing necessary data for calculation) approximated risk ratios as aggressive prostate cancer is a rare event in the general population. However, odds could overestimate the relative risk if evidence shows that aggressive prostate cancer is not a rare event in men with affected relatives, but considering that only 3% of men die *from* prostate cancer, this was unlikely to be observed. Overestimation of risk, if it was found to exist, would be accounted for in interpretation of results and have implication for internal validity. Cross-sectional studies were included as family history can be considered – to a certain degree – to be a constant risk factor. If family history is considered a constant risk factor (genetic predisposition), a cross-sectional study will approximate a longitudinal study. Meta-analyses and systematic reviews were identified and examined for additional references, but were not themselves included in the analysis as doing so would have introduced redundancy and either dilution or magnification of the magnitude of risk.

Use of Observational Studies

Although we included randomized trials in our search strategy (see above), to our knowledge, there have been no randomized controlled trials examining aggressive prostate cancer and family history. Such studies would most likely be designed to compare PSA-based screening to no screening with outcomes of aggressive cancer and mortality. As mentioned previously, our interest is not in determining the utility of screening in this population as it is beyond the scope of this review. Rather, we aim to understand the

magnitude of risk that men with a family history face of dying *from* prostate cancer using aggressive disease as a surrogate. For this purpose, cohort, case-control and cross-sectional studies are valuable.

Additional Criteria (*a priori*)

Studies were excluded if they provided incidence rates or relative risks of particular polymorphisms (e.g. a particular SNP, risk loci on chromosome 8q24 or mutated receptor) without also addressing risk of overall prostate cancer and aggressive prostate cancer. The degree of association and corresponding risk for aggressive prostate cancer and a *specific* genotype—phenotype is beyond the scope of this review. However, studies could still be included if they provided enough information for the reviewer to determine risk of aggressive prostate cancer in those with and without a family history of the disease.

Process of Study Selection

We examined the results from the searches described above by abstract, noting study design, exposure and outcome assessment, and publication date. A second reader did this as well, independently. In an effort to include as many studies as possible for full-text review, exclusions were only made at this stage if it was clear that a study would not answer or was not relevant to our key question. The majority of these excluded studies fell into one of three categories: studies of familial cancers other than prostate cancer, studies of risk factors for prostate cancer other than family history and studies focusing on specific polymorphisms or genotypic permutations. While certainly valuable to understanding the key question, results of this latter category were filed and examined in the later sections (see Genetics of Prostate Cancer, Discussion), but did not contribute to

the evaluation of risk of family history in the general population. At the time of independent review, if either of the reviewers determined that an abstract did not clearly fail to meet eligibility criteria, the entire body of the article was examined. If the reviewers failed to agree on the ability of a study to meet criteria, the entire article was reviewed independently by a senior third reviewer.

Assessment of Quality

Process of Assessment

The quality of the studies included in the review was assessed by criteria developed by the USPSTF for randomized trials and with Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE)⁷³ and criteria outlined by Deeks et al., 2003.⁷⁴ The USPSTF criteria for randomized controlled trials is well established and has been used in the reviews upon which recommendations were made for breast cancer screening with mammography and PSA-based screening for prostate cancer.^{2, 75} The STROBE criteria was developed by a collaborative group including epidemiologists, methodologists, statisticians, researchers and journal editors.⁷³ The Strobe Statement is used in journals such as the Annals of Internal Medicine, Archives of Internal Medicine and the Lancet. The criteria provided by Deeks et al. was used to further characterize internal validity and to ensure that a reasonable degree of continuity existed between quality grades determined through use of the two sets.

Studies were given overall grades of good, fair or poor. While a good study may have limitations, the overall strength of design was such it still produced results that were reliable and valid. Conversely, a poor study was one in which the magnitude of bias was considerable, the results and conclusion were of very low certainty and, therefore, the

study contributed little overall value to the body of literature addressing our key questions. External validity was assessed by examining biological representativeness of the study participants, the size of the population studied, use of protocols for design and accurate use of both exposure status and diagnostic measures. When reviewing quality, we created a separate document with only the study number and author in an attempt to minimize bias due to study population, results or journal title. The STROBE statement and Deeks et al. are included in Appendix. [Note: although we attempted to find randomized trials, we did not identify any with our search. The following describes the components of the quality assessment for observational studies only.]

Assigning Overall Quality Grade

Internal validity and external validity were each given ratings of poor, poor to fair, fair, fair to good, good. Each subsequent category was given a point value (poor=1, poor to fair=2, etc.) The total point value determined the overall quality grade. A perfect hypothetical study would receive a score of 10, the worst hypothetical study would receive a score of 2. Point values and grades were as follows: 5 points or less was POOR, 6 to 7 points was FAIR, and 8 points and above were GOOD. See Table 2 below for further description of scoring grade. Studies that received POOR for both internal and external validity were not included in the quantitative synthesis of outcome assessment. A description of these studies and reasons for grades of POOR for internal and external validity are provided in the Appendix.

Table 2 Grading System for Overall Quality

Point Ranges	Overall Grade
≤5	Poor
6-7	Fair
≥8	Good

Assessment of Internal Validity, Confounding, External Validity

Evaluation of internal validity included assessment of selection, measurement bias, and identification and adjustment for confounding. Selection bias would be minimized in a study with the following characteristics in which the study population resembled the source population. There would also be less risk of selection bias in the studies in which groups (cases, controls; exposed, non-exposed) are similar and maintained with minimal dropouts (or no outcome).

Selection bias would be more pronounced in studies in which the participants were volunteers, recruited with other inadequate sampling method (consecutive assignment, referral for elevated PSA, status post radical prostatectomy or TURP), if participants differed in baseline characteristics, geographical setting, practice setting (specialty clinic, status-post surgery), or if participants refused, were lost to follow-up, or had varying levels of health care access and treatment options. Measurement bias was a considerable concern when developing the quality assessment criteria because of the tendency for measures of TNM System staging, Gleason scores and prostate cancer specific-mortality to change over time.^{50, 51} Family history statuses collected by interview (surveys or in-person) or through medical records were subject to imprecision, but could be minimized by using a combination of methods. Individual methods of questionnaire delivery were subject to different risks of bias. Mailed questionnaires had a high susceptibility to selection bias as these participants had many barriers to successful participation in the study. In person self-reports or in-person questionnaires (likely to have conducted/collected on-site) were less likely to be subject to selection bias, however any retrospectively collected data was vulnerable to recall bias. In-person interviews were considered to be somewhat less susceptible to bias, but more susceptible than methods that cross-

referenced with medical record documentation.^{76, 77} Additionally, men with particularly aggressive cancer (with or without a family history) may be unable to enroll in a study due to severity and rapidity of their disease (thus removing them from the population prior to study recruitment).

Each of our definitions of aggressive prostate cancer was susceptible to unequal, invalid and unreliable measurements, however bias could be minimized by using same measurement between both groups (histology for both aggressive and non-aggressive prostate cancer versus histology for some and cytology for others etc. or using symptoms for metastatic disease such as bone pain versus PET/CT for another group of participants to denote distant spread). Although there is debate in the literature, cytologic and histologic are considered to be comparable in the diagnosis of prostate cancer.⁷⁸ Measurement bias could be minimized by using the same measure for all cases, blinding and with centralized review.

Recall bias was a concern for measurement bias and possibly confounding. Recall bias may act as a confounder because it is related to the exposure and outcome, is not a causal intermediate and is differentially distributed between groups. Recall bias is likely to be more pronounced with retrospective studies and potentially controlled with proper methodology such as measuring family history at baseline rather than at a time after study initiation.

Hyperawareness, hyper-vigilance, and subsequent excessive and or early screening, overdiagnosis (and thus exclusion) and overtreatment may act as confounders in prospective and retrospective studies. Studies that provided well-structured protocol for PSA-based screening and biopsy may minimize this bias. Statistical analyses employing multivariate models may also mitigate confounding.

External validity determined the degree to which the results of a given study could reasonably be considered applicable to the general population of men in the United States with a family history of prostate cancer. External validity would be low if the study population was representative of one small component of the socioeconomic distribution, localized to one geographic location, one ethnicity, consisted of a narrow age range, or included men who were at different levels of risk than men with positive family history in the general United States population. Another concern to external validity was family history exposure in the study population in comparison to the general population, with the exposure potentially over-represented in the study population (and possible source population in specialty clinics for example).

Bias in Study Design

All study designs are subject to bias. Though a good quality randomized trial is likely to have less bias than a cohort, case-control or cross-sectional study, respectively, a well done cohort design may provide more certainty than a poor randomized study. This can be applied to all study designs, however in general, we considered the certainty of results to be greatest to least as the following: randomized studies, cohort, case-control and cross-sectional. Again, because cross-sectional studies measuring exposure of family history had the capacity to approximate a longitudinal study, we did not exclude this design from inclusion. Considering our key question(s) and clear challenges of identifying any randomized studies, we determined that prospective cohort studies would likely be least susceptible to bias, while a poor quality cross-sectional would be most susceptible to bias.

Data Collection

Both reviewers independently examined each article meeting inclusion criteria for characteristics including study design, population, exposure, comparator group, study design, and outcomes. The articles were filed in EndNote and Microsoft Excel (see Appendix).

Data Synthesis

For all included studies, we applied quality criteria described above and extracted data on study population, exposure and outcome (see Appendix). We reported by quality and also by outcome type (TNM Stage, Gleason score, PSA, mortality). Our review does not include a multi-effect meta-analytical review of the literature, however the quality of evidence and results by outcome-type are provided along with a narrative review. Studies of higher quality will be weighted more heavily than studies of poorer quality. For grading the strength of evidence we modified guidelines developed by Owens et al. (AHRQ Series Paper 5, 2010)⁷⁹ for comparing medical interventions.

Study Screening by Title and Abstract

I examined the results from the searches described above by abstract, noting study design, exposure and outcome assessment, and publication date. A second reader did this as well, independently. In an effort to include as many studies as possible for full-text review, exclusions were only made at this stage if it was clear that a study would not answer or was not relevant to our key question. The majority of these excluded studies fell into one of three categories: studies of familial cancers other than prostate cancer, studies of risk factors for prostate cancer other than family history and studies that focused specifically on particular polymorphisms or permutations. While valuable to understanding the key question, results of this latter category were filed and examined in the later sections (see Discussion), but did not contribute to the evaluation of risk of

family history in the general population. At the time of independent review, if either of the reviewers determined that an abstract did not clearly fail to meet eligibility criteria, the entire body of the article was examined. If the reviewers failed to agree on any article's ability to meet criteria, the entire article was reviewed independently by a senior third reviewer.

Study Exclusion by Full-Text Review

We excluded 25 studies at the full-text review stage. Twenty of these 25 studies did not meet eligibility criteria with regards to outcome; they did not report or allow for derivation of aggressive disease. Although the studies evaluated correlation of family history and prostate cancer, the studies did not report characteristics of prostate cancer in such a way that aggressive disease could be assessed. Most of these studies did not report a Gleason, TNM Stage or mortality (etc.) or described characteristics in such a way that limited utility (for example reporting a median PSA, median Gleason etc.).

Results

Search Results

I searched MEDLINE and EMBASE on February 22, 2012 using search strategies developed with the assistance of a library science expert (see Acknowledgements) at Health Sciences Library at UNC-Chapel Hill. Our initial search yielded 8,706 studies (912 studies from MEDLINE and 368 from Embase).

Table 3 Studies included in qualitative and narrative review by nationality		
Authors	Publication Year	Country of Publication
Ahn et al	2008	Finland
Rodriguez et al	1997	United States
Thompson et al	2007	United States
Thompson et al	2006	United States
Makinen et al	2002	Europe*
Yen-Chen et al	2008	United States
Spangler et al	2005	United States
Valeri et al	2000	France
Kotis et al	2002	United States
Schuurman et al	1999	Finland
Rohrmann et al	2003	United States

We added an additional 128 studies through consultation with experts and hand search of the 38 references meeting initial eligibility. A total of 780 studies remained for screening after removing duplicates. A flow chart of our study identification process is described in Figure 2. After screening by title and abstract (described below), a total of 38 studies underwent full-text review. An additional 25 studies were excluded because of an inability to meet our PECOTTS criteria upon closer examination (described below). Thirteen studies met eligibility requirements and were reviewed qualitatively. Of these 13, 2 studies were of poor quality due to poor internal and external validity and/or possessed a “fatal flaw” in methodology. The 11 remaining studies were used in a narrative/quantitative review of the literature to assess our key questions.

Table 4. Summary of Quality Assessment for Included Studies

Authors	Study Design	Internal Validity	External Validity	Overall Grade
Ahn et al	Retrospective Cohort	Fair	Poor to Fair	Fair
Rodriguez et al	Prospective Cohort within a cross-sectional	Poor to Fair	Fair	Fair
Thompson et al (finasteride)	Nested Case-Control	Poor to Fair	Poor	Poor
Thompson et al (placebo)	Nested Case-Control	Fair to Good	Poor to Fair	Fair
Makinen et al	Cross-sectional within a cohort	Poor to Fair	Poor to Fair	Poor
Yen-Chen et al	Retrospective Cohort	Fair	Poor to Fair	Fair
Rohrmann et al	Case-Control	Fair	Poor	Poor
Spangler et al	Case-Control	Poor to Fair	Poor	Poor
Valeri et al	Case-Control	Fair	Poor	Poor
Kotsis	Case-Control	Fair to Good	Poor	Poor
Schuurman et al	Nested Case-Control	Poor	Poor	Poor

Table 5. Results from included studies by study design, quality and outcome type

Authors	Study Design	Outcome Type	Overall Quality	Results
Ahn	Retrospective Cohort	Gleason ≥ 7 , TNM Stage	Fair	RR_{Gleason} Not significant RR_{TNM} 4.16 (2.67-6.49)
Rodriguez	Prospective Cohort within a cross-sectional	Prostate cancer-specific mortality	Fair	RR (by Age) <65: 1.46 (0.80-2.67) 65-69: 1.89 (0.19-2.99) 70-74: 1.90 (1.26-2.87) 75-79: 1.88 (1.27-2.77) ≥ 80 : 1.02 (0.62-1.68)
Thompson (finasteride)	Nested Case-Control	Gleason ≥ 7	Poor	OR_{Gleason} : not significant
Thompson (placebo)	Nested Case-Control	Gleason ≥ 7	Fair	OR_{Gleason} : not significant
Makinen	Cross-sectional within a cohort	Gleason ≥ 7 , T3a, T3b, M1	Poor	RR_{Gleason} 0.6 (0.2-2.0) RR_{TNM} 1.0 (0.3-3.0)
Yen-Chen	Retrospective Cohort	Gleason ≥ 8 , T3b or higher	Fair	RR_{Gleason} 1.74 (1.50-2.02) RR_{TNM} 1.76 (1.37-2.26)
Rohrmann	Case-Control	Gleason ≥ 7 , T3a or higher	Poor	OR_{Gleason} 0.73 (0.45-1.18) RR_{TNM} 0.8 (0.5-1.28)
Spangler	Case-Control	Gleason ≥ 7 , T3a or higher	Poor	OR_{Gleason} 0.79 (0.56-1.12) OR_{T3a} 1.30 (0.89-1.91) OR_{T3b} 1.91 (0.98-3.73) OR_{M1} 1.04 (0.26-4.22)
Valeri	Case-Control	Gleason ≥ 7	Poor	OR_{Gleason} Not significant OR_{TNM} Not significant
Kotsis	Case-Control	Gleason <7	Poor	OR_{Gleason} 1.96 (1.13-3.41)
Schuurman et al	Case-Cohort	Gleason ≥ 7	Poor	RR_{TNM} (fathers) 1.98 (0.93-4.24) RR_{TNM} (brothers) 5.33 (1.36-20.85)*

Table 3. Absolute risk and attributable risk proportion for calculated from cohort studies

Study	Absolute Risk by Outcome Type		Attributable Risk Proportion
Ahn	Gleason AR_{exposed} 0.02 $AR_{\text{non-exposed}}$ 0.01	TNM Stage AR_{exposed} 0.04 $AR_{\text{non-exposed}}$ 0.01	$ARP_{\text{(Gleason)}}$ 5.9 cases over 12 years $ARP_{\text{(TNM)}}$ 17.6 cases over 12 years
Rodriguez	Prostate cancer-death/person-years AR_{exposed} 0.0005; $AR_{\text{non-exposed}}$ 0.0008		ARP 0.04 per 125 person-years
Yen-Chen	Gleason AR_{exposed} 0.010	TNM Stage AR_{exposed} 0.015	ARP_{Gleason} 20.9 cases over 14 years

	AR _{non-exposed} 0.006	AR _{non-exposed} 0.010	ARP _{TNM} 26.2 cases over 14 years
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Synthesis of Study Design and Population

A total of 11 studies were included for quality assessment. Overall, there were 3 cohort studies, 7 case-control studies and 1 cross-sectional study within a cohort. Two of the 3 cohort studies were derived from large-scale, population-based cohorts designed to collect data for multiple purposes. The other cohort was derived from both the intervention and control arm of a randomized controlled study. Notably, none of the cohort studies were designed specifically to answer our key question. However, each provided data for assessment of rate ratios, absolute risk and attributable risk of exposure for our outcome. Three case-control studies and the cross-sectional study were nested in randomized controlled trials. The other 4 case-control studies were single institution-based studies at specialty clinics. As described in Table 3, four of the studies were based in Europe, seven were conducted with participants from the United States.

Demographics

In general, African American men were underrepresented in all of the studies, though study populations within the United States included a small percentage of African Americans (<5%). Men with positive family history tended to be over-represented in case-control studies relative to the general United States population. Prevalence of positive family history in cohort studies more closely approximated that in the general United States population. Two case-control studies consisted only of men aged less than 56. Most study populations had age ranges of 50-70, although the range extended from 40 to over 80 years. A large majority (estimated 70%) of men were between ages 50 and 70. Of note, two of the nested case-control studies were from the intervention and control arm

of a randomized trial. Baseline age of participants and socioeconomic variables were adjusted for in most studies.

Screening Prior to Enrollment

Screening rates prior to enrollment varied within the study populations. The various populations were accounted for in the quality assessment with regards to selection bias (if the study population did not represent the base/source population) and external validity (if either the source or the study population was not comparable to the general United States population). Although only 3 studies specifically address screening, rates are likely predictable based on nationality of the study population. All three studies to address screening rates in the methods section had high screening rates, and other United States study populations also likely had high rates per guidelines existing at that time. One European study was the control arm of the ERSPC trial and thus had no screening. The other European studies also likely had low levels of screening per guidelines. The implications of the various degrees of screening are unclear. For most studies, a prior diagnosis of prostate cancer resulted in exclusion, likely regardless of histologic grade or stage. Because men with a family history are more likely to be screened at an earlier age in the United States, it is possible that this would result in a bias towards the null. However, it is also possible that by excluding men with (most likely – statistically) benign disease from participation, the incidence of aggressive disease within the “exposed” study population would be concentrated and thus cause a bias away from the null. Moreover, the bias is complicated by the unknown impact of PSA-based screening on incidence and mortality of aggressive prostate cancer.

Exposure

Documentation of family history for most of the studies included in the review were by in-person interviews or questionnaires either in-person (given by volunteers) or self-administered. Six studies obtained in-person interview or self-administered questionnaire prior to study enrollment, the remaining 5 (all case-control) collected family history after outcome measure. Five of the 11 studies collected self-administered questionnaires, 4 studies obtained in-person interview or in-person questionnaires. Two of the studies used multiple methods to cross-check family history, one in-person interview and medical records, the other mailed questionnaires and had telephone follow-up.

Outcomes

The outcomes of each study are provided in Table 5. Outcomes for aggressive disease were reasonably comparable across study types and study populations. However, given the variability of diagnostic modalities, screening recommendations and temporal trends, a meta-analysis was felt to be inappropriate due to high risk of imprecision and inaccuracy when coalescing variable characteristics.

Gleason Score

Nine studies reported aggressive disease by Gleason score. Of these, 2 of the studies were cohort, 7 were case-control and 1 was cross-sectional. Nine of the studies defined aggressive prostate cancer as greater than or equal to 7. One study reported aggressive Gleason as greater than 7. Overall, 2 studies reported increased relative risk of aggressive disease in men with affected first-degree relative compared to men without positive family history and 8 studies reported no statistical significance.

Of the 2 cohort studies, 1 reported a risk ratio of 1.74 (1.50-2.02), the other reported no statistical significance. Both cohort studies were fair quality. For cohort

reporting increased relative risk (Yen-Chen et al.), we calculated a risk difference of 0.004 and an attributable risk of 20.9 cases over 14 years. All 6 case-controls studies reported no statistical difference for odds of aggressive cancer defined by Gleason. One of these case-control studies was of fair quality, five were poor quality. One fair quality cross-sectional study within the ERSPC cohort also reported no statistical significance.

Summary Report for Gleason

- Two cohort studies; one fair quality reports increased relative risk, one fair quality reports no difference
- Six case-control studies; one fair and five poor quality report no difference,
- One cross-sectional; fair quality reports no difference

TNM Stage

Seven of the included studies reported aggressive disease by TNM Stage. Of these, 2 were cohorts, 4 were case-control and 1 was cross-sectional. Overall, 3 studies showed family history was significantly associated with aggressive prostate cancer. Two cohort studies, Ahn et al. showed relative risk of 4.16 (2.67-6.49) and Yen-Chen et al. reported relative risk of 1.76 (1.37-2.26) of aggressive cancer for men with an affected first-degree relative compared to men without family history. We calculated absolute risk for Ahn et al. of 0.04 for aggressive disease in the exposed compared to 0.01 in the non-exposed, corresponding to an attributable risk of 17.6 cases over 12 years. For Yen-Chen et al., the absolute risk in the exposed and non-exposed was 0.015 and 0.010, respectively, for TNM defined aggressive disease. We calculated the risk of aggressive disease attributable to positive family history to be 26.2 cases over 14 years.

One poor quality case-cohort reported odds of reported relative risk of 5.33 (1.36-20.85) for men with affected brothers, but no significance for men with affected fathers. Three poor quality case-control studies and one fair quality case-cohort study reported no statistically elevated risk for aggressive disease defined by T3 overall, T3a, T3b and metastatic disease compared to men without family history.

Summary Report for TNM Stage

- Two fair quality cohort studies show increased risk – relative risk of 4.16 and 1.76, absolute risk difference of 0.03 and 0.005, attributable risk of 17.6 cases over 12 years and 26.2 cases over 14 years
- One poor quality case-cohort shows increased risk, three poor quality case-control and one fair quality cross-sectional study show no increase risk

PSA Levels at Diagnosis

One poor quality case-control (Norrish) study reported PSA levels of 20ng/mL or more at the time of diagnosis. Authors found PSA of 20 ng/mL or more to be less common in men with family history of prostate cancer than in men without such history. However, the study had several important limitations and was excluded from analysis (Table XXXX).

Summary Report for Pretreatment PSA

- One case-control study met eligibility, but was excluded due to poor quality

Prostate Cancer-Specific Mortality

One fair quality cohort study reported prostate cancer-specific mortality (Rodriguez). Authors reported relative-risk of prostate cancer-specific mortality, but not

absolute risk. Relative risk of prostate cancer-specific mortality was higher in men aged 70-74 and men aged 75-79 with family history of prostate cancer compared to men without such history. However, there was no difference in relative risk for men aged less than 70 and more than 79 years. We calculated a risk difference of 0.0003 and an attributable risk of 0.04 per 125 person-years for aggressive disease given positive family history.

Summary Report for Prostate Cancer-Specific Mortality

- One fair quality cohort showed increased relative risk for men ages 70-79, risk difference was small (0.0003) for all ages included, attributable risk of 0.04 per 125 person-years

Summary of Overall Outcomes

- All 3 cohort studies showed some increase in risk for at least a subset of the study population, however the risk difference and attributable risk was small.
- Seven non-cohort studies showed no increase in risk magnitude, 1 showed increased risk for men with affected brothers but not fathers.

Synthesis of Evidence

We found patterns in the evidence reported by included studies. Cohort studies were more likely to report increase risk and non-cohort studies more likely to show no difference in risk. Gleason-defined outcomes were more likely to show no difference than TNM-defined outcomes. Studies with specialty clinic populations were all case-control studies and were more likely have smaller numbers, report no difference and have shorter follow-up. Cohort studies were more likely to be more representative of the general

population of men and have longer follow-up. Studies with longer follow-up were more likely to report increased risk, but for all of these studies the absolute risk of the exposed was similar to that of the non-exposed. There was a concern that Gleason- and TNM-defined aggressive cancer would show increased incidence rates in later studies compared to earlier studies (due to upward migration and increased use, capacity of imaging technology), however the extent to which this was evident is unclear.

Strength of Evidence

Risk of Bias

Although observational studies are generally considered inferior to randomized trials in hierarchy of study design to assess effect of a “risk factor,” a methodologically conscientious cohort or case-control study has the potential to produce unbiased results. In the 11 studies included in the quantitative assessment, 3 were cohort, 7 were case-control and 1 was cross-sectional. Application of quality criteria yielded 3 fair quality cohort studies, 1 fair and 6 poor case-control studies and 1 fair quality cross-sectional study. We did not set an *a priori* minimum percentage of good, fair or poor quality studies to determine low, medium or high risk of bias. However, given our knowledge of study quality and critical appraisal, we concluded that 55% poor, 45% fair and 0% good quality most likely denotes a high risk of bias in the evidence.

Consistency

Consistency was determined by examining the effect size – whether most or all studies fell on the “same side” of the null with regard to the outcomes. If the most or all of the studies reported an effect (a positive association of risk), consistency was also

determined by the range of the effect size. A narrow range of effect size would denote consistency while a wide range of effect size would indicate inconsistency.

Of 9 studies reporting Gleason score, 1 showed increase in relative risk, 8 showed no difference. Of 7 studies reporting aggressive disease by TNM Stage, 3 showed increase in relative risk, 4 showed no difference. The 1 study reporting PSA was excluded. The study reporting prostate cancer-specific mortality showed increased relative risk for men aged 70-79.⁸⁰

In summary, the evidence is inconsistent. While Gleason-based outcomes were more consistent in proving the null, it did not do so for one fair quality cohort. TNM Stage was determined to be inconsistent. Only one study reported prostate cancer-specific mortality and it showed only increased risk for one men aged 70-74 and 75-79. Of note, screening in this group has previously been found to have less benefit than harm.⁸¹ Therefore, overall the evidence was felt to be inconsistent.

Directness

In adopting our criteria for “aggressive” prostate cancer, we designed our review to be limited with regard to directness. Although Gleason scores of 7, 8 or more and TNM Stage T3 or above have been shown to be associated with greater risk of death from prostate cancer,^{51, 82} the predictors themselves are intermediates or surrogates for clinically important outcomes (in this case prostate cancer-specific mortality or overall mortality). Ten of 11 included studies reported only clinical intermediates. Prostate cancer-specific mortality, though superior to the other surrogates, is also inferior to overall mortality with regard to directness. Overall, the evidence is indirect.

Precision

The degree of certainty for the estimates of effect or lack thereof determines precision and precise estimate is one which is clinically useful. With regard to Gleason and TNM Stage, we feel there is a high degree of certainty that – in the absence of clinical or patient-specific context – a man reporting family history of prostate cancer in a first-degree relative is not in and of itself a reasonable justification to consider that man to be at increased relative risk of aggressive – clinically significant – prostate cancer compared to a man without such a family history.

Plausible Confounding

Observational studies examining effect of family history and aggressive disease have risk of confounding that may work in a direction opposite to the observed effect. This would occur in the form of hyper-awareness, artificial over-estimation of risk perception, overdiagnosis and overtreatment of relatively benign disease that is *not* clinically significant in regards to morbidity or mortality. A large percentage of men who have histologic prostate cancer will never have clinically significant disease. Men with affected relatives are more likely to start PSA-based screening earlier and more often. Considering the inaccuracy of the PSA test, men with positive family histories are more likely to receive biopsy with increased frequency of PSA-based screening. Because histologic prostate cancer that is clinically insignificant is prevalent – men with family history are more likely to receive diagnosis of prostate cancer and therefore will not meet criteria for inclusion of studies examining family history and prostate cancer. The men with affected relatives who do not receive diagnoses of prostate cancer therefore, may represent a population in which the frequency of benign disease is concentrated, thus moving the observed effect towards the null.

Conversely, confounding could also exist that works away from the null. Certain prostate cancers are aggressive and it is reasonable to speculate that there are genetic components to this (and all) cancers. Aggressive prostate cancers may be less likely to be detected with regular PSA-based testing, while less aggressive cancers may be more likely to be detected. Thus, men with affected relatives who may have higher a likelihood of aggressive disease may be over-represented in the population (because men with less aggressive disease have been excluded with PSA-based screening) and cause an amplification of an effect that is away from the null.

Publication Bias

Publication bias is a concern in any systematic review. For this and most reviews, publication bias would most likely have a tendency to move the observed effect away from the null. However, because family history of prostate cancer has been considered a clinically reliable risk factor for overall prostate cancer since 1960,⁸³ it may be that a publication bias would actually favor the null. See the Discussion for further details and methods we used to address and minimize publication bias.

Discussion

In our review of the literature, we found that the evidence on relative and absolute risk of aggressive prostate cancer in men with a positive family history in at least one first-degree relative is mixed. Furthermore, the quality of evidence examining the relationship of family history and aggressive disease is poor to fair overall.

Summary of Evidence

Eleven studies were included in the narrative assessment. Three studies were cohort studies, each was of fair quality. Evidence from the cohort studies on Gleason-

defined, TNM-defined and prostate cancer specific mortality is mixed. We calculated absolute risk and attributable risk for studies reporting increased relative risk for aggressive disease in men with affected relatives compared to those without; we found absolute risk difference and attributable risk to be small and unlikely to change the benefit-to-harms ratio described by the USPSTF regarding the general population (see Clinical Implications).² Seven case-control (1 fair, 6 poor quality) and one fair quality cross-sectional study also report mixed findings, but most show no statistically significant increase in risk magnitude of aggressive prostate cancer for men with a family history. The evidence indicates that if it exists, the magnitude to which men with affected first-degree relatives are at increased risk for aggressive prostate cancer is likely small.

Congruency with Existing Literature

As mentioned in the introduction, four formal meta-analyses and two informal reviews have assessed the relationship between overall prostate cancer and family history. In contrast to previous reviews, this review exclusively assesses risk associated with only aggressive prostate cancer. All previous reviews have found men with family history to have increased relative risk for prostate cancer than men without family history. Importantly, reviews by Bruner⁹ and Zeegers⁷ stratify risk of having an affected brother or father and Johns⁶⁷ stratifies by number of affected first-degree relatives when assessing evidence on *overall* prostate cancer. We did not stratify our results in this review and discuss the clinical implications of this below (see Clinical Implications).

Overall, we found that evidence of increased risk of *aggressive* prostate cancer in men with a family history is incongruent with evidence of increased risk of *overall* prostate cancer and family history.

Congruency with Recommendations of Professional Societies

Importantly, our review informs but does not evaluate PSA-based screening in men with at least one affected first-degree relative. However, we extrapolated our finding in terms of implication for such screening modalities. In doing so, we found the evidence to be incongruent with current recommendations from the American Urology Association and the American Cancer Society which encourage men with a positive family history to undergo screening at an earlier age. Our review is congruent with the United States Preventive Services Task Force recommendation against PSA-based screening in men with a positive family history. While previous systematic reviews and meta-analyses show that a positive family history is associated with increased risk for *overall* prostate cancer, we have found inadequate evidence that the association persists for *aggressive* prostate cancer. As described in the Introduction, men with a family history significant for prostate cancer are more likely to undergo earlier and more frequent screening compared to men without such history.⁸⁴ This tendency may be attributable to recommendations from these professional societies and or an increased anxiety or awareness of prostate cancer. As a result of these factors, men with a positive family history may be more likely to suffer harms of overdiagnosis and overtreatment than men in the general population (see Clinical Implications).

Congruency with Other Commentaries

Several authors have suggested risk stratification to determine whether and how frequent men should receive PSA-based screening.^{13-15, 69, 85} Family history is a component of risk calculators that attempt to estimate risk of prostate cancer on biopsy. Our review

of the evidence is incongruent with use of family history in risk calculators or in risk stratification schemes.

Limitations of the Review

Publication Bias

Our review has several limitations. Publication bias is a common short-coming of systematic reviews and if present would tend to push our findings away from the null (see Strength of Evidence). To evaluate for publication bias, we searched for unpublished abstracts in both the American Society of Clinical Oncology and Genitourinary International Symposiums from 2000 to 2012. We identified one unpublished abstract from the 2005 ASCO Annual Meeting reporting an earlier age at diagnosis in black men with a positive family history in at least one first-degree relative; however, we were not able to determine whether criteria for aggressive disease was met.⁸⁶ It is unlikely that additional unpublished data would provide convincing evidence to change our conclusion.

Variable Populations

As described in our introduction, this review is limited in that it does not report evidence on relative or absolute risk for men with *more* than one first-degree relative. Discussed in further detail in the Introduction and Clinical Implications sections, the genetics of prostate cancer are complex and incompletely understood. Several studies have reported differences in risk depending on type of first-degree relative, with many describing higher risk in brothers compared to fathers.⁹ Although, this may be attributable to increased awareness for men whose sibling rather than father has been diagnosed with prostate cancer, other factors may also play a role.

We also did not define criteria for age at diagnosis in first-degree relative. In not defining age criteria for family history, our review is at risk of differential *misclassification* of family history in that we may have considered a family history to be positive even if the first-degree family member was diagnosed at an advanced age at which rates of overdiagnosis are highest.^{87, 88} We considered including only those studies that provided age of diagnosis of 70 years or less in the first-degree relative. However, we determined that this restriction presented a risk of narrowing our search that was greater than the potential benefit of minimizing a bias toward the null. Our review was also limited in that it did not describe risk of African American men with positive family history. African American men are underrepresented or not represented in all of the studies included in this review.

Another limitation is the variability of the study populations of included (and excluded) studies, not only by geographic location within the United States, but internationally as well. We considered excluding studies on populations outside of the United States *a priori*, however we determined that this would not be a reasonable course of action due to the fact that the results from the ERSPC Trial, conducted exclusively in European countries, have had implications for screening practice recommendations in the United States. There was also variability in prior screening throughout included study populations. Higher rates of screening prior to study enrollment would most likely cause a bias towards the null, as men who had been previously diagnosed with prostate cancer were generally excluded or unable to participate. However, as discussed in Strength of Evidence, there is also a potential for bias in the direction away from the null.

Clinical Intermediates and Follow-Up

Use of clinical intermediaries is another limitation. Although Gleason Score, TNM Stage and PSA at time of diagnosis are correlated with disease aggressiveness and therefore mortality, they are not necessarily clinically meaningful in and of themselves. Only one of the included studies reported prostate cancer-specific mortality and there were no studies reporting magnitude of risk for overall mortality.

Follow-up Time

Follow-up time was also a limitation of this study. The median follow-up time for the 11 studies included in narrative assessment varied. For cohort studies the follow-up tended to be 9 years or longer, but for non-cohort studies it tended to be fewer than 9 years. Overall, prostate cancer is an indolent disease and as a result follow-up periods less than 10 years may not be adequate to assess differences in outcomes. However, it is likely that aggressive prostate cancer is not indolent and therefore studies with shorter follow-up may be needed to assess our key question.

Harms

The most important limitation with regards to *clinical* application was inability to assess harms (see Clinical Implication). Overall, we found insufficient evidence to consider family history as a risk factor for aggressive prostate cancer. If men with a family history in the general population are not at increased risk for aggressive disease, they may be at *high-risk* for suffering harms from prostate cancer screening in the form of earlier overdiagnosis and overtreatment due to unsubstantiated increased risk perception. Thus, frequency of harm outcomes may be amplified in men with affected relatives and the harms may outweigh the benefits of PSA-based screening to an even greater extent than in the general population. However, while this review does not find sufficient

evidence of increased risk, it also did not find sufficient evidence for no increase in risk (see Clinical Implications).

Clinical Implications

Although there is robust evidence that family history increases relative risk for *overall* prostate cancer, the evidence is insufficient to extend this or any increase in risk to *aggressive* prostate cancer without further characterization of a man's "positive" family history. In other words, the benefits are likely to be outweighed by the harms if screening is recommended for a man reporting a positive family history if the clinician does not obtain number and age of diagnosis in affected family members, relatedness of affected family members and the clinical characteristics (if possible) of the affected family member's prostate cancer (age at diagnosis and cause of mortality). Because of the magnitude of overdiagnosis of prostate cancer in the PSA-era, men with family history of clinically *insignificant* prostate cancer are at a high risk for overestimating perception of risk, suffering harms as a result of earlier and more frequent screening and unnecessary treatment in the absence of evidence showing *either* increase risk of aggressive cancer or ability of PSA-based screening to provide benefit if an increase risk exists.

Clearly, Bayesian probability will play a role in any man reporting more than one first-degree relative with prostate cancer even in the absence of further characterization, as this could indicate familial inheritance patterns. Importantly, this review considers evidence supporting increased risk of aggressive prostate cancer in the "general population with a positive family history." Family studies have demonstrated 5- and 11- fold increase risk of *overall* prostate cancer in men with two or three affected first-degree relatives compared to men without such history, respectively.^{24, 89} Studies have also reported

increase risk for *overall* prostate cancer in men carrying BRCA1 or BRCA2 mutations.⁹⁰

However, as described in the introduction, the study of prostate cancer genetics, while rapidly developing, appears to be many years from validating predisposition for aggressive disease, determining prevalence and assessing benefits and harms of PSA-based screening in these populations.

Potential Protective Mechanism for Patients

A potential mechanism to protect patients from overdiagnosis and overtreatment of clinically insignificant prostate cancer secondary to positive family history would be to require further qualification for a family history to be considered positive. Similar to measures used in cardiovascular disease (men should begin screening at earlier ages if they have a family history of serious cardiovascular event prior to age 50 etc.), such qualifications could entail follow up questions to elicit age of diagnosis of first-degree relative and if the affected relative died *from* or *with* the disease. If employed in conjunction with clinician intuition and judgment, such a mechanism may protect patients who have had a first-degree relative diagnosed with clinically *insignificant* prostate cancer from harms of overscreening, overdiagnosis and overtreatment.

Implications for Future Research

An important area for further exploration include basic science and translational research with aims to delineate the distinction of a family history of “overdiagnosed” prostate cancer from a family history of clinically significant, or *aggressive* prostate cancer. It follows intuitively, in the context of our evolving understanding of cancer biology, that there may be certain forms of prostate cancer that are both *aggressive* and

heritable. Perhaps the presence of such subtypes in some, but not other populations contributes to the mixed evidence presented in this review.

As described in the USPSTF recommendation statement and discussed in the Introduction, this review is one component of potential screen-based preventative measures. If there are groups of men who, upon further research, are found to have *aggressive* subtypes of prostate cancer that are also heritable, we would also need randomized controlled trials of PSA-based screening in these groups to determine the magnitude of mortality benefit – if one exists – and if it outweighs risk of harms. One concern is that aggressive tumors are either too rapidly progressive to be detected with annual or biennial PSA-based screening or that the tumors are undifferentiated and do not produce PSA thus limiting the usefulness of PSA-based screening. Alternatively, randomized controlled trials are also needed to determine if screening all men with a *fully-characterized* family history of *aggressive* prostate cancer in a first-degree relative – even without further elucidation of aggressive cancer subtypes – would provide benefits that outweighed harms of screening.

A final area of considerable importance for future research is further characterizing the harms of prostate cancer screening including patient anxiety (labeling, active surveillance, biopsy), anxiety, pain and complications of biopsy, and likelihood and consequences of unnecessary treatment. A systematic review of the literature to determine the evidence of harms of prostate cancer screening would be especially important for men with a family history as it is likely that these men represent a particularly vulnerable group in whom the harms of screening may be concentrated.

Conclusion

In this review we assessed the evidence for our key question:

What is the relative and absolute risk of *aggressive* prostate cancer in men with at a family history of prostate cancer in at least one first-degree relative compared to men without such history?

We found that there is mixed, poor and overall insufficient evidence that men with a positive family history are at an increased risk of *aggressive* – clinically significant – prostate cancer relative to men without such history.

Furthermore, we feel that as a result of this evidence, the benefits of PSA-based screening in these men without further characterization of the number, age of diagnosis and clinical impact of the affected first-degree family member is unlikely to outweigh risk of harms. Due to the potential overestimation of perceived risk, men with a “poorly characterized” positive family history of prostate may represent an especially vulnerable population at high-risk for harms of overdiagnosis and overtreatment.

Acknowledgements

We would like to thank Mellanye Lackey in Library Sciences at the Health Sciences Library at UNC-Chapel Hill for helping us with our search.

Appendix 1

Table 4 – Description of reasons for exclusions based on quality

Study	Reason For Exclusion – Fatal Flaws
Cerhan et al., 1999	Number of cases of aggressive prostate cancer is too low to contribute in a meaningful way (n=2). Statistical models adjusted for variables for unclear reasons in assessing aggressive disease, the degree of uncertainty was substantial given lack of power and the poor statistical methodology
Norrish et al., 1999	No description of statistical methodologies or

	adjustments for age or other covariates described; Power is insufficient for aggressive disease (n=3).
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Table 5. Outcomes by type, quality, study design

Author, year	Source	Study	Exposure
Ahn et al, 2008	The Alpha-tocopherol, beta-carotene cancer prevention Study	19,652 male smokers aged 50–69 years in southwestern Finland	Self-report with baseline questionnaire prior to entry
Rodriguez et al., 1997	508,576 males in the Cancer prevention study (ACS) enrolled by volunteers in all 50 states in 1982	481,011 men with no prior history enrolled by volunteers	In-person questionnaire given by volunteers at set times during original study
Thompson et al., 2006	18,882 men 55 or older with normal DRE and PSA less than 3 randomly assigned to finasteride or placebo for 7 years	5519 men from the placebo group who underwent biopsy at end of study or due to rising PSA	In-person interview at time of biopsy
Thompson et al., 2007	18,882 men 55 or older with normal DRE and PSA less than 3 randomly assigned to finasteride or placebo for 7 years	N=5,675 from 9459 randomized to finasteride arm who underwent biopsy at end of study or due to rising PSA	In-person interview at time of biopsy
Schuurman, et al 1999	58,279 men 55-69 from 204 municipalities in Finland (data from the Netherlands Cohort Study (assessing diet and cancer)). ⁹¹	Cases were men with overall prostate cancer at 6.3 years, controls were randomly sampled from cohort	Self-administered questionnaire at baseline
Yen-Chen et al, 2008	51,529 male health professionals in the Health Professionals Follow-Up Study	Subcohort of the HPFS study; 42,144 participants provided data on family history; medical history	Questionnaire; follow-up questionnaires, medical records; interview of family members
Spangler et al, 2005	Men in Pennsylvania aged 40 and over diagnosed with prostate cancer	All participating men diagnosed with prostate cancer at the UPHS (PENN) urologic oncology department clinics	In-person interview after referral
Makinen et al., 2002	80,000 men aged 55 to 67 from the population register from 1996-1999; part of the	20,311 men randomized to the screening arm	Self-administered questionnaire

	ERSPC (the finish center)		(prior to screening)
Kotsis et al., 2002	Middle aged men with access to health care and well-connected to specialists, recruited to study	Men less than 55 referred to University of Michigan for participation in the Prostate Cancer Genetics Project.	Questionnaire, follow-up with medical records;
Valeri et al, 2000	Men in France referred to urology departments for newly diagnosed prostate cancer	801 consecutive CaP probands treated in three French urology departments between 1994-1997	In-person interview after referral
Rohrmann et al., 2003	Men in the Baltimore area diagnosed with prostate cancer who underwent radical prostatectomy between 1992 and 1999	498 of 1,544 consecutive men who underwent radical prostatectomy with a single surgeon who were under the age of 55	Mailed questionnaire to all 498 men with follow-up telephone reminder

Figure 3. Independent description of study population, eligibility criteria and quality

Ahn et al., 2008⁹²	
Study Design	Retrospective Cohort
Source Population	The Alpha-tocopherol, beta-carotene cancer prevention Study; a placebo-control study; 29,133 eligible middle aged male smokers in Finland
Inclusion Criteria	Male age 50-69 volunteered to be randomized between 1985 and 1988. Unable to obtain access to original methodology
Exclusion Criteria	History of any malignancy other than non-melanoma cancer of skin or carcinoma in situ, severe angina, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, anticoagulant therapy, other medical problems that might limit participation and any use of the following supplements - vitamin E, vitamin A, beta carotene
Study Population	19,652 men aged 50–69 years in southwestern Finland who smoked at least 5 cigarettes per day men with complete data from the original trial; No specific reference to screening in groups; prior screening likely minimal, intra-study screening likely minimal (European nationality)
Risk Factors Consistent Between Groups	No appreciable differences between groups (exposed, non-exposed); both groups appear to have same risk of developing outcome
Attrition	High (>20%) and Unequal (>15%): 52% of non-exposed, 95% of exposed had outcome measurements at 19 years overall follow-up (unable to identify median follow-up for non-exposed or overall cohort)
Measurement of	Self-report of participants prior to entry

exposure	
Measurement of outcomes	Cases were ascertained by Finish Cancer Registry during the study follow-up, with additional centralized record reviews through April 1999. Medical records of each prostate cancer case diagnosed through April 1999 were centrally reviewed by 2 study oncologists to confirm the diagnosis and stage. In addition, the histopathologic and cytological specimens of the cases were reviewed by study pathologists during the trial and post-trial periods (56% of total cases).
Statistical Analysis	Appropriate; Person-time was calculated from the return date of the family history questionnaire (1991) to the date of prostate cancer diagnosis, death or April 30, 2003, whichever came first; age-adjusted. Rate ratios determined with Cox proportional hazard models; multivariate analysis for confounders.
Internal Validity	Fair
External Validity	Poor-Fair
Overall	Fair

Rodriguez et al., 1997⁸⁰	
Design	Prospective cohort within a cross-sectional survey
Source Population	508,576 males in the Cancer prevention study (ACS) enrolled by volunteers in all 50 states in 1982; purpose of the Cancer Prevention Study II was to assess mortality related to cancer
Inclusion Criteria	Completion of questionnaire
Exclusion Criteria	Excluded for incomplete racial data (2,399), personal history of prostate cancer (3,303), other cancer (21,863)
Study Population	481,011 men with no prior history enrolled by volunteers across all 50 states, DC, Puerto Rico who agreed to participate and successfully completed the questionnaire. Median age was 57, 75% between 47-70, none younger than 30.
Risk Factors Consistent Between Groups	Considerable differences seen in exercise between exposed and unexposed; however age was not described. No difference with regard to race, religion, sibship, education, vasectomy, BMI, smoking history, vegetable consumption, fat consumption
Attrition	<5% at 9 years follow-up; follow-up equal in both groups
Measurement of exposure	Questionnaire given by volunteers; defined by 1) any reported family history of prostate cancer in father or brother, father only, brother only, by number of affected first-degree relatives, age of affected family member diagnosis (before and after age 65)
Measurement of outcomes	Blinding uncertain. Vital status and cause of death of study participants was determined using two approaches: volunteers making personal inquiries in 1984, 1986, 1988, automated linkage using the National Death Index used to complete follow-up through 1991. ICD-9 indicating prostate cancer as underlying cause. Nine

	years may be inadequate to observe outcome
Statistical Analysis	Cox proportional hazards modeling to compute rate ratios; adjusted for potential risk factors, stratified by age, controlled for race; accounted for sibship size and age of diagnosis.
Internal Validity	Poor-Fair
External Validity	Fair
Overall	Fair

Thompson et al., 2006⁴⁷	
Study Design	Nested case-control
Source Population	18,882 men 55 or older with normal DRE and PSA less than 3 randomly assigned to finasteride or placebo for 7 years ³¹
Inclusion Criteria	55 years old or older and had a normal DRE and a PSA level less than or equal to 3 ng/mL.
Exclusion Criteria	Clinically significant coexisting conditions, AUA symptom score over 20
Study Population	5519 men from the placebo group who underwent biopsy, had at least one PSA measurement and DRE within the year before the biopsy and had at least two PSA measurements performed during the 3 years before biopsy; 17% positive family history, 96% white, 91% with 5-7 PSA screens
Risk Factors Consistent Between Groups	Unable to determine distribution of age/baseline characteristics in cases or controls, or exposed versus non-exposed
Attrition	<5%
Measurement of exposure	Family history obtained by interview at time of biopsy
Measurement of outcomes	Gleason - central pathologist, no mention of blinding
Internal Validity Grade	Fair-Good
External Validity Grade	Poor-Fair
Statistical Analysis	Multivariate – adjusted appropriately; identified/addressed interaction terms
Overall	Fair

Thompson et al., 2007⁹³	
Study Design	Nested case-control
Source Population	18,882 men 55 or older with normal DRE and PSA less than 3 randomly assigned to finasteride or placebo for 7 years; ³¹
Inclusion Criteria	All participants who underwent biopsy at any of seven annual visits, including end-of-study biopsy; AUA symptom score less than 20.

Exclusion Criteria	Clinically significant coexisting conditions, AUA symptom score over 20
Study Population	N=5,675 from 9459 randomized to finasteride arm who had at least one PSA measurement and DRE within the year before the biopsy and had at least two PSA measurements performed during the 3 years before biopsy; 93% white; 83% had 7 or more PSA screens; 86% had 7 or more DREs, 96% had been on finasteride for at least 5 years.
Risk Factors Consistent Between Groups	Unable to determine distribution of age/baseline characteristics in cases or controls, or exposed versus non-exposed
Attrition	22% - unable to determine from which group
Measurement of exposure	Family history obtained by interview
Measurement of outcomes	Biopsy with rising PSA or at end of study; notably, PSA threshold levels for biopsy were lowered to account for effect of finasteride (bias toward null); Gleason – central pathologist, no mention of blinding
Internal Validity Grade	Poor-fair
External Validity Grade	Poor
Statistical Analysis	Multivariate – adjusted for confounders
Overall	Poor

Schuurman et al., 1999⁹⁴	
Study Design	Nested Case-Control
Source Population	58,279 men 55-69 from 204 municipalities in Finland (data from the Netherlands Cohort Study (assessing diet and cancer)). ⁹¹ The cohort included 58,279 men and 62,573 women ages 55-69 years at the start of the study.
Inclusion Criteria	Completion of baseline questionnaire
Exclusion Criteria	Prevalent cancer at baseline other than skin cancer and subjects with incomplete or inconsistent dietary data according to criteria.
Study Population	Study Cases: 642 men with overall prostate cancer at 6.3 years (median follow-up) Study Controls: 1688 (random sample of the cohort – randomized selection process unclear) Cases of advanced prostate cancer: 213 Cases of local prostate cancer: 226
Risk Factors Consistent Between Groups	Unable to determine comparability of exposed/non-exposed, cases/controls
Attrition	High: TNM Stage available for only 35%
Measurement of exposure	Self-administered questionnaire at baseline
Measurement of outcomes	Cancer registries and/or TNM staging/clinical staging; Stage determination unclear; no blinding mentioned
Internal Validity	Poor-Fair
External Validity	Poor-Fair

Statistical Analysis	Adjusted for age, age at diagnosis, race; subgroup analysis for advanced disease; power may not be adequate; case-cohort approach for analysis for calculation of cancer incidence rates, the number of cases for the entire cohort was used as the numerator, while person years at risk (denominator) were estimated using a random male sample of controls, the subcohort (N = 1688).
Overall	Poor

Yen-Chen et al., 2008⁹⁵	
Study Design	Retrospective Cohort
Source Population	51,529 male health professionals (Health Professionals Follow-Up Study (HPFS) – dentists, optometrists, osteopaths, podiatrists, pharmacists, veterinarians aged 40-75
Study Population	Subcohort of the HPFS study; 42,144 participants provided data on family history; medical history; highly screened population with 8 years follow-up (84% screened at least once in non-exposed, 92% in exposed); assessed with follow-up questionnaires, if permission granted authors searched hospital records and pathology reports
Inclusion Criteria	Completion of baseline questionnaire
Exclusion Criteria	Prior prostate cancer; excluded clinical stage T1a
Comparison of groups (exposed, non-exposed; cases, controls)	Age, race socioeconomic variables comparable between exposed and unexposed; exposed group had higher prior PSA-screening rates and
Attrition	26%; Gleason available for 2,718 cases (74%); TNM Stage available for 2,603 (70.4%);
Measurement of exposure	Questionnaire; follow-up questionnaires, medical records; interview of family members
Measurement of outcomes	TNM Stage and Gleason through medical records and pathology review; risk of bias due to exclusion of T1a cancers (authors' attempt to reduce overdiagnosis of indolent cancer); approximately 90% of the 3,695 cases using medical records and pathology reports; remaining 10% per family interview; follow-up period may be inadequate to assess outcome; blinding unknown;
Internal Validity	Fair
External Validity	Poor-Fair
Statistical Analysis	Stratification by age, covariates adjusted for included vigorous physical activity, cigarette smoking, tomato sauce, calcium, alpha-linolenic acid, fish, red meat. Did not report model adjusted for age, race. Concern for adjustment of clinically insignificant risk factors.
Overall	Fair

Spangler et al., 2005⁹⁶	
Study Design	Case-control

Source Population	Men in the Pennsylvania aged 40 and over, diagnosed with prostate cancer
Inclusion Criteria	Prostate cancer (incident diagnosis)
Exclusion Criteria	Prior cancer diagnosis, at any site, except non-melanoma skin cancer, self-reported current use of finasteride, or were non-incident prostate cancer cases (diagnosed more than 12 months before study ascertainment. No date of diagnosis in EMR; no knowledge of family history
Study Population	All participating men diagnosed with prostate cancer at the UPHS (PENN) urologic oncology department clinics between 1995-2002; mean age 60.6; N=684
Comparison of groups (exposed, non-exposed; cases, controls)	Cases (Gleason):281, Controls: 272; Cases (T3a): 147, Controls: 446 Cases(T3b): 37 Controls: 559; Cases (M1): 9 Controls: 653 Cases defined as evidence of metastatic disease on MRI Unable to determine characteristics of cases versus controls (age, race) Selected from same population, but may not have same risk of overall and aggressive prostate cancer (risk of selection bias)
Attrition	High – approximately 50% for each outcome
Measurement of exposure	In-person interview; positive family history was first or second degree relative with prostate cancer
Measurement of outcomes	TNM staging (TNM did not include Nodal status and is thus less valuable.) Gleason - from surgical pathology reports.
Internal Validity	Poor-Fair
External Validity	Poor
Statistical Analysis	Odds-ratios with logistic regression models – adjusted for confounders; power may be insufficient to assess certain outcomes
Overall	Poor

Makinen et al., 2002⁹⁷	
Study Design	Cross-sectional within cohort (screened arm of a randomized controlled trial)
Source Population	“Nested” cohort with ERSPC, ⁴ approximately 80,000 men aged 55 to 67 from the population register from 1996-1999; part of the ERSPC (the finish center);
Inclusion Criteria	Men who provided baseline information (age, family history etc.)
Exclusion Criteria	Prior diagnosis of prostate cancer
Study Population	20,311 men randomized to the screening arm; 964 (4.7%) with FH; all men in this arm were referred for biopsy if PSA was 4 or over, 1996-1999 – 3 years follow-up
Comparison of groups (exposed, non-exposed; cases, controls)	Unable to discern differences between exposed and non-exposed; median age of diagnosis is comparable however baseline/median age or range of age is not available
Attrition	<5%
Measurement of	Self-administered questionnaire (prior to screening); prevalence of

exposure	family history <5% (approximates general US population)
Measurement of outcomes	Men with PSA over 4.0ng/mL received biopsy; TNM Stage, Gleason Score
Internal Validity	Poor-Fair
External Validity	Poor-Fair
Statistical Analysis	Stratified by family history, no mention of adjustments for confounders, no reference to covariates; Student T-Tests to compare age at diagnosis, Wilcox rank to determine relative risk of aggressive cancer
Overall	Poor

Kotsis et al., 2002⁹⁸	
Study Design	Case-control
Source Population	Middle aged men with access to health care and well-connected to specialists, volunteering to be referred. Men aged less than 56 years; Men in the Michigan University area and beyond are referred to University of Michigan for participation in the Prostate Cancer Genetics Project.
Inclusion Criteria	Recent diagnosis of prostate cancer at 55 or younger
Exclusion Criteria	Unknown family history, missing pre-diagnosis PSA, race other than white or black, pathology report of metastasis, enrollment following enrollment of blood relative
Study Population	Men less than 55 (median age 51, range 34-51) diagnosed with CaP and participated in study cohort between years 1995-1999. Referred to University of Michigan for participation in the Prostate Cancer Genetics Project. Cases = 133, Controls = 126 same population, may not have same risk of developing outcome at baseline (risk of selection bias); screening status not specifically described, but likely high in both cases and controls; potentially higher in exposed than unexposed
Comparison of groups (exposed, non-exposed; cases, controls)	Unable to determine comparison of cases, study designed to determine association of family history and overall prostate cancer
Attrition	10%; unable to determine distribution of attrition in cases and controls
Measurement of exposure	Questionnaire and confirmed by medical records; did not differentiate first-degree from 2 nd degree for predicting aggressive cancer
Measurement of outcomes	TNM Stage, Gleason
Internal Validity	Fair-Good
External Validity	Poor
Statistical Analysis	Adjustments for confounders; logistic regression for odds of Gleason less than 7

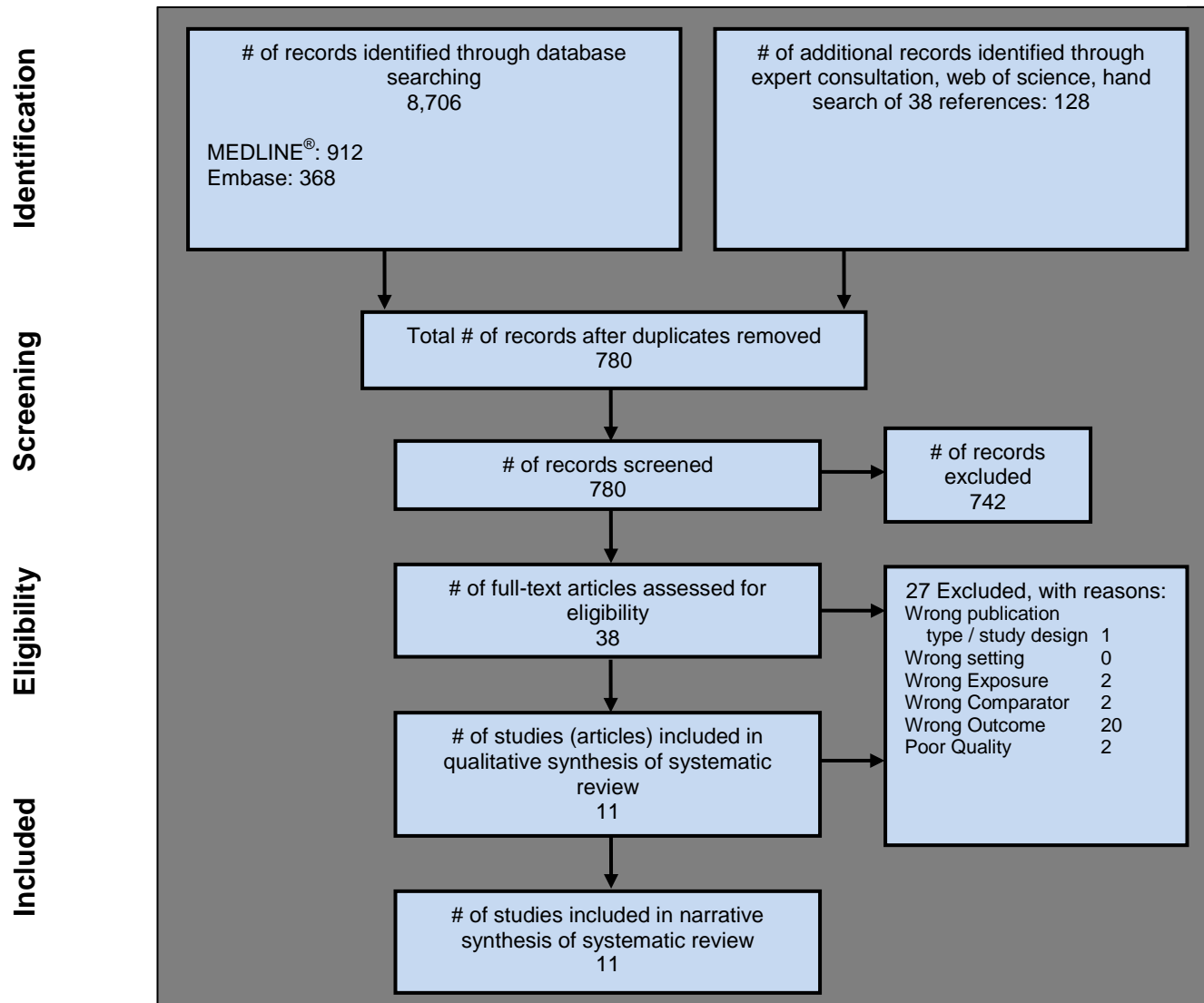
Overall	Poor
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Valeri et al., 2000⁹⁹	
Study Design	Case-control
Source Population	Men in France referred to urology departments for newly diagnosed prostate cancer or who had previously been known to have prostate cancer in the 1990s.
Study Population	801 consecutive prostate cancer probands treated in three French urology departments between 1994-1997. Cases: Men with aggressive prostate cancer defined by TNM Stage III (T3N0M0) or IV (T4/xN0/xM0/x) or Gleason of 7 or more. Controls: men with not aggressive prostate cancer given above definitions.
Inclusion Criteria	Unable to determine detailed inclusion criteria
Exclusion Criteria	Unable or unwilling to provide family history
Comparison of groups (exposed, non-exposed; cases, controls)	Does not appear to be any appreciable difference between cases and controls with regard to exposure; otherwise unable to compare cases and controls. Unable to determine prior screening or presence of symptoms in cases versus controls.
Attrition	30%; multivariate analysis performed on 189/267
Measurement of exposure	In-person interview; sporadic 1 prostate cancer in relative, hereditary (one first) with 2 or more after age 55; familial (two first-degree), at least 1 after age 55
Measurement of outcomes	TNM Stage, Gleason Grade (no central review, no blinding mentioned)
Statistical Analysis	Multivariate analysis was performed on 189/267 comparing hereditary and sporadic (odds-ratio)
Internal Validity	Fair
External Validity	Poor
Overall	Poor

Rohrmann et al., 2003¹⁰⁰	
Design	Case-control
Source Population	Men in the Baltimore area diagnosed with prostate cancer who underwent radical prostatectomy between 1992 and 1999
Study Population	498 of 1,544 consecutive men who underwent radical prostatectomy with a single surgeon who were under the age of 55 Cases: men found to have Gleason score of 7 or more on review of surgical pathology or (T3a) extraprostatic extension Controls: men found to have Gleason of less than 7 or those without extraprostatic extension (T3a)
Inclusion Criteria	Age less than 55, cancer diagnosed and surgery performed in study time period.

Exclusion Criteria	Age 55 or more
Risk Factors Consistent Between Groups	Age is not comparable between exposed and not exposed in terms of age at surgery ($P < 0.01$) but we do not have numerical representation of this difference. We also do not know if age is comparable between cases and controls; mean pre-operative PSA is higher in men without family history.
Attrition	27% did not return the questionnaire, unclear distribution between cases and controls
Measurement of exposure	Mailed questionnaire to all 498 men with follow-up telephone reminder;
Measurement of outcomes	Gleason and extraprostatic extension determined by surgical pathology
Statistical Analysis	Logistic regression to estimate odds ratio of high grade disease in men undergoing radical prostatectomy for prostate cancer who reported a positive family history; stratified race (though did not report) and for age at surgery as follows: less than 47, 47-49.9, 50-51, 52-53.9, 54-54+. Used age at surgery as surrogate for age at screening. Tested for multiplicative interaction with cross-product (age-BMI). Wald test for significance; age stratification and identification of interaction terms in logistic model.
Internal Validity Grade	Fair
External Validity Grade	Poor
Overall	Poor

Figure 2 – Flow diagram of search



APPENDIX 2

Search strategy for PubMed:

(medical history taking OR family history OR familial OR hereditary) AND risk factors
AND (Prostatic Neoplasms OR prostate cancer) AND (prostate neoplasm/epidemiology
OR Prostatic Neoplasms/genetics OR Prostatic Neoplasms/mortality OR Age Factors OR
genetic predisposition to disease OR Tumor Markers, Biological/blood OR prostate-
specific antigen/blood OR predictive value of tests OR prostatic neoplasms/prevention &
control OR medical history taking/statistics & numerical data OR risk assessment OR
follow-up studies OR retrospective studies OR prospective studies OR Cohort studies OR
retrospective cohort studies OR prospective cohort studies OR incidence OR father OR
brother) 781 results

Limits to the above search were applied and included humans, male, clinical trial, meta-analysis, randomized-controlled trial, adults aged 19 years and over published between 1992 and 2012. (96 studies). Of note, the date of 1992 was selected because it coincided with widespread clinical acceptance and use of the prostate specific antigen level as a potential screening tool for prostate cancer. The above search was adapted with the help of the research librarian for the Embase database. Studies were also identified through hand searches of reference lists from studies that met inclusion criteria, systematic reviews and meta-analyses obtained from the search in addition to expert recommendations* (Paul Godley, Ronald Chen).

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